

# Neoadjuvant chemoradiotherapy followed by surgery is associated with better survival outcomes in patients with locally advanced esophageal squamous cell carcinoma

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Chemoradiotherapy (CRT) is one of the most effective treatments to be expected to cure esophageal cancer of any stage. Esophageal squamous cell carcinoma (ESCC) is more sensitive to CRT than adenocarcinoma. Even in T4 stage ESCC, definitive CRT shows an excellent complete response (CR) rate of up to 52% (1,2). In addition, esophagectomy for ESCC is highly invasive and correlates with frequent postoperative morbidity and mortality. Thus, CRT is widely administered as treatment for ESCC, even when other treatments are considered more appropriate.

Standard treatment for locally advanced ESCC is neoadjuvant therapy followed by esophagectomy. As a neoadjuvant therapy, CRT and chemotherapy are common in Western and Eastern countries, respectively (3,4). A randomized controlled trial (RCT) that prospectively compared long-term outcomes between neoadjuvant CRT plus surgery (trimodality) and surgery alone (the CROSS trial) suggested that the former was associated with significantly better prognostic outcomes than the latter (5). In the study, ESCC showed better survival outcomes (5-year survival rates greater than 50%) than those of adenocarcinoma after trimodality treatment. Meanwhile, a phase II study regarding definitive CRT for locally advanced ESCC (JCOG 9906) showed a 5-year survival rate of 36.8% (6). Thus, as Barbetta *et al.* mentioned, neoadjuvant CRT plus surgery has become the standard of care for locally advanced disease. However, they also documented that only 5% of patients with locally advanced

esophageal cancer received trimodality therapy, and most patients (49%) were treated with definitive CRT in the United States. Thus, the authors conducted the current study to elucidate the superiority of trimodality therapy to definitive CRT on prognostic outcomes in patients with locally advanced ESCC. To resolve several statistical issues due to the retrospective design in this study, the authors used a propensity score-matching method, which can strengthen the reliability of the current results.

As a result, prognostic outcomes of trimodality therapy surpass those of definitive CRT. Both overall and disease-free survivals were preferable in the trimodality group, and in particular, the local recurrence rate was considerably lower in the trimodality group (trimodality 0%, definitive CRT 38%). Consequently, they concluded that neoadjuvant chemotherapy followed by surgery is the optimal treatment for locally advanced ESCC. Previous influential studies also supported the current result (7-9). Interestingly, incidences of regional and systemic recurrence were statistically equivalent between the trimodality and definitive CRT groups, implying that definitive CRT is insufficient to control ESCC locally.

It is noteworthy that pathological examination of surgical specimens after neoadjuvant CRT showed a good pathological CR rate of 47%. If we can preoperatively identify pathological CR using any reliable modality, we can avoid unnecessary highly invasive surgery after CRT. Despite advances in modalities for examination, it remains

an unresolved important clinical issue (10). In this study, the authors documented that even with negative endoscopic examination results, benign histological findings on biopsy, and significantly decreased maximum standardized uptake value on positron emission tomography after treatment, up to 30% of patients harbored remnant disease in their esophagus. It is of great concern whether the watch-and-wait strategy, which is effective for rectal cancer with clinical CR after neoadjuvant CRT, is also applicable to esophageal cancer (11).

Despite solid statistical analysis, this study has several limitations. This study recruited only patients who completed CRT. Patients with progressive disease from the end of neoadjuvant CRT to surgery were excluded. Those can confer selection bias. In addition, the chemotherapy regimen changed during the study period. The duration of this study (17 years) was also long, which can correlate with historical biases regarding modalities for diagnosis, surgical procedures, and peri-treatment management.

However, this study is considered clinically important because they concluded the prognostic superiority of trimodality therapy for stage II and III ESCC using reliable statistical methods equivalent to prospective RCT. The current results are reasonable and acceptable, when compared with previous studies with similar settings (7-9). Taking those results into account, we can conclude that neoadjuvant CRT followed by surgery is currently the optimal treatment for locally advanced ESCC.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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